REMARKS

Overview

The Examiner is thanked for her careful review of the application and the June 5, 2006 Response and for withdrawing objections and rejections she had previously made (Office Action, ¶¶ 1 and 2).

In this paper, we discuss the invention and the new claims, list the art relied on by the Examiner, and discuss the various objections and rejections.

The Invention

As the Examiner will recall, the present invention relates to, among other things, assays for the detection and/or quantification of human MDA-modified LDL (malondialdehyde-modified low density lipoprotein) and human OxLDL (oxidized low density lipoprotein) in samples derived from the blood or tissues of human beings, the MDA-modified LDL and OxLDL containing at least 60 substituted lysine moieties per apo B-100 (apolipoprotein B-100) moiety. The antibodies used are mAb-4E6, which is specific for both analytes but not native LDL, and optionally mAb-8A2, which binds with both analytes as well as native LDL (see application, e.g., page 6, line 8, to page 7, line 32).

The invention satisfies a number of needs, among them, the need for non-invasive tests (i.e., assays) that are highly specific for the analytes of interest (i.e., human MDA-modified LDL and human OxLDL). See application, e.g., page 3, lines 7-23.

The New Claims

All pending claims (56-74) have been cancelled and new claims 75-84 added. Claim 75 is the only independent claim, is analogous to cancelled claim 56, and concerns an assay for an analyte of human MDA-modified LDL and human OxLDL using monoclonal antibody mAb-4E6 and optionally also monoclonal antibody mAb-8A2. Thus, for example, mAb-4E6 could be used alone in a competitive assay to detect the analyte in the sample (see, e.g., application, page 7, lines 17-32) or the two antibodies could be used in a sandwich assay to detect the analyte (see, e.g.,

application, page 7, lines 5-16). The analyte is in a sample "derived from" human blood or human tissue. Use of "derived from" is believed to be perfectly appropriate, as set forth below in the discussion of ¶ 8A of the Office Action.

New claims 76-79 find support in the application as filed (see, e.g., page 5, lines 25-34). New claims 80-81 find support in the application as filed (see, e.g., page 7, lines 17-25). New claims 82-83 find support in the application as filed (see, e.g., page 7, lines 5-16). New claim 84 finds support in the application as filed (see, e.g., page 3, lines 28-33).

The Art Relied On By The Examiner Discussed In This Response

- Liu

Liu K, Cuddy TE, Pierce GN, "Oxidative status of lipoproteins in coronary disease patients," American Heart Journal (1992), volume 123, pages 285-290.

- Haberland

Haberland ME, Fogelman AM, Edwards PA, "Specificity Of Receptor-Mediated Recognition Of Malondialdehyde-Modified Low Density Lipoproteins," *Proc. Natl. Acad. Sci USA*. 1982; 79: 1712-1716.

- Palinksi

Palinski W, Horkko S, Miller E, Steinbrecher UP, Powell HC, Curtiss LK, Witztum JL, "Cloning of Monoclonal Autoantibodies to Epitopes of Oxidized Lipoproteins from Apolipoprotein E-deficient Mice," Journal of Clinical Investigation (1996), volume 98, pages 800-814.

- Winzor

Winzor DJ, De Jersey J, "Biospecific Interactions: Their Quantitative Characterization And Use For Solute Purification," Journal of Chromatography (1989), volume 492, pages 377-430.

- Kotani

Kotani K, Maekawa M, Kanno T, Kondo A, Toda N, Manabe M, "Distribution Of Immunoreactive Malondialdehyde-Modified Low-Density Lipoprotein In Human Serum," Biochimica et Biophysica Acta 1994; 1215: 121-125.

- Kondo (EP 0 484 863 A1)

Akira Kondo is the first-named inventor of EP 0 484 863 A1 (applicant: Daiichi Pure Chemicals Co.). This document was discussed at length in the June 5, 2006 Response (see, e.g., pages 12-18), and is there referred to as "Daiichi" or "Daiichi EP 0 484 863."

Office Action, ¶¶ 3, 4, and 5 – formal matters

Applicants thank the Examiner for reviewing the art they made of record and for returning all of the PTO-1449 forms submitted with the original Information Disclosure Statement (filed with the application) and with the first four Supplemental Information Disclosure Statements to evidence such consideration.

A Fifth Supplemental Information Disclosure Statement was mailed to the PTO on August 23, 2006 and, therefore, was not in front of the Examiner at the time the current Office Action was mailed (on August 22, 2006). The only document cited in the Fifth Supplemental Information Disclosure Statement, JP Laid Open Patent Application (Kokai) No. 4-173096, corresponds to Kondo (EP 0 484 863 A1), which is already of record in this case and which the Examiner has cited. *Applicants assume the Examiner will initial and return the PTO-1449 form for the Japanese document in due course.*

Office Action, ¶ 6 – objection – updating to reflect issuance of patent

In ¶ 6 of the Office Action, the Examiner asks that page 1 of the application be updated to include a reference to U. S. Patent No. 6,727,102. Applicants believe that has already been done. Please see page 5 of the June 5, 2006 Response, where the "Related Applications" paragraph, originally added by means of the Preliminary Amendment filed with the application on March 17, 2004, was further amended to read "This application is a continuation of U.S. Patent Application No.

09/446259, filed December 20, 1999, now U.S. Patent No. 6,727,102 ..." (emphasis added).

Office Action, ¶ 7 – objection – wording in claims 56-60

The Examiner asserts that "[t]he claims recite an 'antibody with high affinity *contain* at least XXX substituted lysine moieties'" and "that a term is missing from the claim language..." (emphasis in original).

The part of the claim to which the Examiner is apparently referring is the last paragraph of claim 56, which reads as follows (emphasis added):

> wherein the MDA-modified LDL and OxLDL for which the first antibody has high affinity contain at least 60 substituted lysine moieties per apo B-100 (apolipoprotein B-100) moiety.

Applicants believe that if the Examiner further considers this language, she will agree that (i) the plural subject of the verb "contain" is "MDA-modified LDL and OxLDL"; (ii) the term "for which the first antibody has high affinity" describes the subject "MDA-modified LDL and OxLDL"; and (iii) the term "for which the first antibody has high affinity" is not the subject of the verb "contain."

Applicants note that claim 1 of parent U. S. Patent No. 6,727,102 contains the same wording (at column 30, lines 35-38).

Applicants have cancelled claims 56-60 and the new claims do not contain the language to which the Examiner objected; however, even if they did, applicants believe that on reconsideration, the Examiner would agree that the language was in fact not objectionable.

Office Action, ¶ 8A – rejection – claim 73 – § 112 – alleged indefiniteness

The Examiner asserts that in claim 73 (which specified that "the sample is derived from the body fluids of a human being") "the use of the term 'derived' is indefinite."

MPEP § 2173.02 states that

> [t]he test for definiteness under 35 U.S.C. 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). [*Id.* at 2100-212]

In other words, the legal standard for definiteness is whether a claim reasonably apprises those of skill in the art of its scope. *In re Warmerdam*, 31 USPQ 2d 1754, 1759 (Fed. Cir. 1994). The cancelled claims certainly did that. MPEP § 2173.02 mandates how definiteness should be determined:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. [*Id.* at 2100-211]

That those skilled in the art know what "derived" means cannot be denied. "Derived" has been used in tens of thousands of patents, including *parent* U. S. Patent No. 6,727,102 (e.g., claim 18: "The assay of claim 1 in which the sample is derived from the body fluids of a human being").

In addition to parent patent US 6,727,102, numerous other US patents have expressed and utilized the concept of materials such as samples being derived from fluids or tissues. See, e.g., U. S. Patent Nos. 7,132,509 ("sample derived from a tissue other than the colon"), 7,122,328 ("'Samples,' ... include tissue culture derived fluids"), 7,094,561 ("derived from uterine tissue or lymphoid tissue"), 7,057,019

("physiologically derived fluids"), 6,991,916 ("suitable samples may include extract tissues such as testis or brain or from neoplastic growths derived from such tissues"), 6,953,680 ("Samples ... include organ or tissue culture derived fluids"), 6,894,146 ("immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from these tissues"), 6,887,974 ("physiologically derived fluids"), 6,673,551 ("samples of DNA or cDNA derived from tissues"), 6,617,116 ("samples include ... biologically derived fluids"), 6,524,327 ("body derived fluids"), 6,437,102 ("derived from biological materials" and "blood-derived products"), 6,337,195 ("sample derived from a tissue other than the colon"), 6,312,931 ("biologically derived composition"), 5,683,916 ("fluid derived from cell culture supernatant or ascites fluid"), 5,547,576 ("biologically derived substance" and "blood, plasma, serum and urine, liquid culture medium of cell and microorganism or a solution containing protein component derived from these fluids"), 5,482,841 ("The biological sample will generally be blood derived, usually in the form of plasma or serum"), 5,321,123 ("blood, plasma, plasma-derived fluids" and "blood, plasma and plasma derived products"), 5,296,356 ("A sample liquid is, in particular, understood as body fluids or fluids derived therefrom. Body fluids include, for example, blood or urine. Sample liquids derived from these fluids are, for example, those which can be obtained by dilution or concentration of these fluids or by addition or removal of particular components from the fluid, for example serum or plasma."), 5,011,608 (sample contains a compound "derived from the fluids and tissues of vertebrates, invertebrates or plants"), 4,963,265 ("blood derived fluids"), and 4,456,550 ("derived from fluids that are biologically generated").

In other words, those skilled in the art, from a time well before the filing of the present application and up through the present, have had no difficulty in understanding what a sample derived from tissues or fluids was.

Consistent with that long-standing knowledge in the field, the application uses exactly the same type of language found in those patents and refers to "samples, e.g., samples derived from body fluids (like plasma or serum) or tissues" (application, page 3, lines 32-33). Samples used in the application include treated arterial specimens (application, page 12, line 37, to page 13, line 5; page 14, lines 5-24),

treated plasma samples (application, page 16, lines 12-16), and treated venous blood samples (application, page 21, lines 9-16). The exemplified treatment includes submerging in PBS containing sucrose, antioxidants, and EDTA, freezing, diluting in PBS containing antioxidants, EDTA, and other compounds, and centrifuging.

Application claim 73 specified that the "sample is derived from the body fluids of a human being." As an example, body fluids include the blood of a human being. Removing a portion of that blood to use as a sample would be deriving that sample "from the body fluids of a human being." Adding an anti-coagulant to that sample to prepare a different sample would be "deriving." Removing the blood cells from that sample to prepare a plasma sample would be "deriving." Removing the clotting proteins from the plasma sample to prepare a serum sample would be "deriving." All of those samples would have been "derived from the body fluids of a human being" and one skilled in the art would readily know that.

To reject a claim under the second paragraph of 35 USC § 112, "[i]t is incumbent on the [E]xaminer to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims. *Ex parte Wu*, 10 USPQ2d 2031, 2033 (BPAI 1989). This the Examiner has not done. The Examiner has not made any factual determination establishing that one of ordinary skill in the art "would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims" because of the use of "derived."

Cancelled claim 73 was definite, just as claim 18 of parent patent US 6,727,102 is definite. New claim 75, which specifies that the sample is "derived from the blood or tissue of a human being," is definite and should not be objected to.

Office Action, ¶ 8B – rejection – claim 56 – § 112 – alleged vagueness and indefiniteness

The Examiner has rejected claim 56 as allegedly being vague and indefinite because "the term 'capable' does not positively limit the claim language." The Examiner relies on *In re Hutchinson*, 69 USPQ138 (CCPA 1946), for support.

Applicants respectfully point out that claim 56 did not contain the word "capable"; the only claim containing that word was claim 74 ("The assay of claim 56 in which at least one antibody is capable of detecting ...").

First, the case relied on by the Examiner, *In re Hutchinson*, is irrelevant. Second, those skilled in the art understand what "capable of" means and claim 74 reasonably apprised those of skill in the art of its scope and, therefore, was not "vague and indefinite." Third, the United States Patent and Trademark Office knows that "capable of" is perfectly acceptable: many thousands of issued US patents use "capable of" in their claims (including parent patent US 6,727,102 – see claim 19) and, in fact, the MPEP indicates that "capable of" is perfectly acceptable.

As to the first point, i.e., *In re Hutchinson* being irrelevant, the CCPA was dealing with article claims, not method claims (and applicants' claim 74 was not an article claim). Furthermore, in *In re Hutchinson*, the term in question ("adapted for") was in the "introductory clause," i.e., the preamble (69 USPQ at 141). As is clear from the CCPA decision, *In re Hutchinson* concerned whether a limitation in the *preamble* of a claim "constitute[d] a limitation in any patentable sense" (*id.*). In applicants' claim 74, "capable of" was not in the preamble.

As to the second point, as noted above, MPEP § 2173.02 at 2100-212 states that

> [t]he test for definiteness under 35 U.S.C. 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986).

Applicants believe "capable of" would readily be understood by one skilled in the art, and the Examiner has not alleged it would not be. For this reason alone the rejection is unsound.

To reject a claim under the second paragraph of 35 USC § 112, "[i]t is incumbent on the [E]xaminer to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims. *Ex parte Wu*, 10 USPQ2d 2031, 2033 (BPAI 1989). This the Examiner has not done. The Examiner has not made any factual determination establishing that one of ordinary skill in the art "would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims" because of the use of "capable."

As to the third point, the United States Patent and Trademark Office knows that "capable of" is perfectly acceptable. "Capable of" is used in many tens of thousands of issued US patents and it has been used for many decades, including in the expression "capable of detecting," the expression used in applicants' claim 74. See, e.g., U. S. Patent Nos. 7,135,561 ("2. An isolated infectious BVDV clone, capable of serving as a template for transcription ...."), 7,135,102 ("1. ... sensor capable of detecting the completion ...."), 7,122,659 ("1. ... a fluorescently labeled phosphorylatable compound which is capable of being phosphorylated ...."), 6,950,011 ("14. ... a tire pressure monitoring device capable of detecting wheel movement ...."), 6,867,013 ("10. ... antisense molecules capable of blocking transcription or translation of mRNA ...."), 6,771,173 ("1. ... personnel presence sensor capable of detecting the distance ..."), 6,608,037 ("4. ... a nitroreductase capable of activating CB1954."), 6,501,382 ("1. ... an antenna capable of detecting electromagnetic signals ...."), 6,376,653 ("3. A hybridoma capable of secreting the antibody of claim 1."), 6,198,398 ("1. ... moisture sensor capable of detecting the moisture level ...."), 6,172,049 ("33. ... an expression vector, capable of expressing a polypeptide ...."), 5,977,457 ("5. ... plants capable of expressing all the morphological and physiological characteristics ...."), 5,817,290 ("18. ... a nucleic acid test region capable of integration into the DNA ...."), 5,646,264 ("1. ... capable of intercalating dsDNA ...."), 5,605,797 ("15. An oligonucleotide probe capable of detecting a mutation ...."), 5,413,791 ("1. ... reactive groups capable of forming a covalent ether bond ...."), and 4,882,033 ("1. An electrochemical device capable of detecting an amount of unburned components ....").

MPEP § 2173.05(g) indicates that "capable of" is acceptable:

> A functional limitation is an attempt to define something by what it does, rather than by what it is (e.g., as evidenced by its specific structure or specific ingredients). There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). [*Id.* at 2100-219]
>
> It was held that the limitation used to define a radical on a chemical compound as "incapable of forming a dye with said oxidizing developing agent" although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought. *In re Barr*, 444 F.2d 588, 170 USPQ 33 (CCPA 1971). [*Id.* at 2100-220]

Obviously if "incapable of" is "perfectly acceptable" (the CCPA's words), "capable of" is also perfectly acceptable.

Applicants have cancelled claim 74 and the new claims do not contain the language to which the Examiner objected; however, even if they did, applicants believe that on reconsideration, the Examiner would agree that the language was in fact not objectionable.

Office Action, ¶¶ 9, 10, and 11 – rejection – claims 56-74 – § 112 – alleged lack of written description and enablement

Applicants strongly disagree with the Examiner's reasoning but to hasten allowance are amending the claims (without prejudice) to moot the written description and enablement rejections.

New independent claim 75 specifies that monoclonal antibodies mAb-4E6 and optionally mAb-8A2 are used and that the sample is derived from the blood or tissue of a human being, and dependent claim 84 specifies that the sample is a plasma or serum sample.

As discussed above, consistent with the knowledge of those skilled in the art, the types of samples that can be used are broadly disclosed and enabled in the application. Thus, the application teaches the use of "samples, e.g., samples derived from body fluids (like plasma or serum) or tissues" (application, page 3, lines 32-33). The examples show use of treated arterial specimens (application, page 12, line 37, to page 13, line 5; page 14, lines 5-24), treated plasma samples (application, page 16, lines 12-16), and treated venous blood samples (application, page 21, lines 9-16).

Applicants believe the new claims are fully described and enabled and should not be rejected as were the prior claims. Applicants also note that the Examiner stated in the Office Action at page 8 that applicants "provide[] guidance for blood sampling to assay for MDA-modified LDL and OxLDL ...."[1]

Office Action, ¶¶ 12, 13, and 14 – rejection – claims 56-74 – alleged non-statutory double patenting based on US 6,309,888 in view of Liu and Haberland

In the previous (January 30, 2006) Office Action, the Examiner rejected all claims for alleged obviousness-type double patenting based on U. S. Patent No. 6,309,888. In the June 5, 2006 Response, applicants explained why they believed the Examiner was wrong. In the current Office Action, the Examiner has again rejected all claims for alleged obviousness-type double patenting based on U. S. Patent No. 6,309,888 in view of Liu and/or Haberland. As explained in MPEP § 804 at 800-11 to 800-12:

> There are generally two types of double patenting rejections. One is the "same invention" type double

[1] The Examiner goes on say that "no other samples are contemplated or tested in the instant disclosure," but that is not so. Applicants clearly do test tissue samples. See, e.g., application, page 12, line 37, to page 13, line 5, and page 14, lines 5-24, which disclose testing arterial specimens.

> patenting rejection based on 35 U.S.C. 101 which states in the singular that an inventor "may obtain a patent." The second is the "nonstatutory-type" double patenting rejection based on a judicially created doctrine grounded in public policy and which is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinguishing from claims in a first patent.

There would certainly be no "prolongation of the patent term" here (compare cancelled claim 56 and new claim 75, on the one hand, with claim 1 of the 6,309,888 patent, on the other), and applicants continue to vigorously disagree with the Examiner's conclusion and reasoning; however, to hasten allowance of this application, applicants are filing herewith a terminal disclaimer. As pointed out in MPEP § 804.02 at 800-32, "[t]he filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection," citing *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991). There the CAFC indicated that filing the disclaimer "raises neither a presumption nor estoppel on the merits of the rejection."

Office Action, ¶ 15(l) – rejection – claims 56, 61-71, and 73 – § 102(a) – alleged anticipated based on Palinski and Winzor

The Examiner asserts that Palinski "disclose[s] methods for producing antibodies specific for binding LDL," that "[s]ome E0 antibodies generated for binding to malondialdehyde-LDL (MDA) also bind or recognize copper oxidized LDL,"[2] and that "[t]he antibodies were used to detect LDL levels in plasma." The Examiner also points to other features allegedly present in Palinski. The plain fact is, however, that Palinski

[2] What the Palinski Abstract says is that "some E0 antibodies selected for binding to malondialdehyde-LDL also recognized copper oxidized LDL, acrolein-LDL, or LDL modified by arachidonic or linoleic acid oxidation products" (emphasis added) and not just copper oxidized LDL.

does not anticipate. It did not anticipate cancelled claims 56, 61-71, and 73, and it does not anticipate pending claims 75-84.

"To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383, 58 USPQ2d 1286, 1291 (Fed. Cir. 2001); *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991)." *Brown v. 3M*, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001).

However, Palinski fails to disclose or even suggest numerous claim limitations. For example, Palinski's antibodies do not bind with both human MDA-modified LDL and human OxLDL, and Palinski's antibodies are not applicants' mAb-4E6 or mAb-8A2 (or anything nearly as good as those antibodies). Thus, independent claim 56 (now cancelled) was not anticipated and neither is new independent claim 75.

Careful review of Palinksi reveals that the antibodies initially selected for binding to copper oxidized (non-physiological) LDL do not bind to MDA-modified LDL and the antibodies initially selected for binding to MDA-modified LDL do not bind to copper oxidized LDL, with one exception, E013; however, when Palinski tested E013 against human blood, it did not bind even as much as the control. In other words, Palinski does not disclose any antibodies that can detect both human MDA-modified LDL and human OxLDL.

Palinski characterized thirteen antibodies, which were originally selected for recognition of either copper oxidized LDL or MDA-modified LDL (page 803, right column, first full paragraph). Those antibodies are E01, E02, E03, E04, E05, E06, E07, E09, E011, E012, E013, E014, and E017, which are listed in Figure 3, panels A and B, and used to produce the test results reported in panels A to F (page 804).

Figure 2 (page 803) shows the results of a competitive radio immunoassay in which 16-hour copper oxidized LDL is the plated antigen and antibody E04 with or without a competing antigen is brought into contact with the substrate. The competitors included MDA-modified LDL (data points shown with black circles), 4-hour

copper oxidized LDL (black, upwardly pointing triangles), and 16-hour copper oxidized LDL (black, downwardly pointing triangles).

The x-axis of Figure 2 shows the number of nanograms of competitor introduced. Use of enough 16-hour copper oxidized LDL as the competitor results in complete inhibition, which is to be expected since E04 was originally selected for its binding to 16-hour copper oxidized LDL (page 803, right column, last paragraph). As noted above, in Figure 2, the data points for 16-hour copper oxidized LDL are represented by black, downwardly pointing triangles, and the point at which 50% inhibition occurs ($B/B_0 = 0.50$) is at about 200 ng. The volume of competitor solution was 25 µl (page 802, left column, third full paragraph). Assuming an average molecular weight of about 3,500,000 for copper oxidized LDL, which is a reasonable assumption (see US Patent Application Publication No. 2002/0090389, page 12, right column), the affinity of E04 for copper oxidized LDL is calculated to be about 4×10^8 M^{-1}, far lower than the affinities of mAb-4E6 and mAb-8A2 for OxLDL (application, page 6, line 7 et seq.).[3]

In Palinski Figure 3, panel A, the plated antigen is copper oxidized LDL and the curves show the ability of antibodies E01, E02, E03, E04, E05, E06, E07, and E09 (all of which were originally selected for their binding to copper oxidized LDL) to compete with labeled E04 for binding to the copper oxidized LDL on the substrate (in other words, solutions of each of the antibodies and labeled E04 were contacted with the substrate – Figure 3, caption). As shown by the similar shapes of the curves, all of the antibodies were able to compete effectively (page 804, left column).

In Palinski Figure 3, panel B, antibodies E011, E012, E013, E014, and E017 (which were originally selected for their ability to bind to MDA-modified LDL or native LDL) were tested the same way, i.e., for their ability to compete with labeled E04 for binding to the copper oxidized LDL on the substrate. As is apparent from the curves,

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[3] Some investigators have reported lower molecular weights for LDL (e.g., values of 2,600,000 to 3,100,000), but using such lower molecular weights would result in calculating even lower affinities. MDA-modified LDL and OxLDL are not believed to have molecular weights significantly different from the literature value of 3,500,000 for LDL.

none of them except for E013 competed (page 804, sentence bridging left and right columns).

In Palinski Figure 3, panel D, the plated antigen is MDA-modified LDL and the curves show the ability of antibodies E01, E02, E03, E04, E05, E06, E07, and E09 (all of which were originally selected for their binding to copper oxidized LDL) to compete with labeled E014 for binding to the MDA-modified LDL on the substrate. As shown by the curves (and as expected), none of them was an effective competitor (page 804, right column).

Palinski Figure 3, panel E shows the ability of E011, E012, E013, E014, and E017 (which were originally selected for their ability to bind to MDA-modified LDL or native LDL) to compete with labeled E014 for binding to the MDA-modified LDL on the substrate. As shown by the curves (and as expected), E012, E013, E014, and E017 were effective competitors, but E011 (originally selected for binding to native LDL) competed poorly (page 804, right column, through page 805, left column).

These four panels together (panels A, B, D, and E) show that only E013 was able to bind to both MDA-modified LDL and copper oxidized LDL.

However, as shown in panel E of Figure 3, E013's affinity for MDA-modified LDL is essentially the same as E014's affinity for MDA-modified LDL. In panel E, the point at which 50% inhibition for E014 occurs ($B/B_0 = 0.50$) is at about 1000 ng, and that allows us to estimate E014's affinity for MDA-modified LDL as about $9 \times 10^7\ M^{-1}$, far lower than the affinities of mAb-4E6 and mAb-8A2 for MDA-modified LDL (application, page 6, line 7 et seq.). Furthermore, Palinski Figure 9 (page 811) shows what happens when E013 is used to try to detect *human* OxLDL: it can't. E013 produced fewer counts (flashes) than the mouse IgM that was used as a control.

To repeat: Palinksi antibodies that bind to copper oxidized (non-physiological) LDL don't bind to MDA-modified LDL and Palinski antibodies that bind to MDA-modified LDL don't bind to copper oxidized LDL, with one exception, E013; but when tested against human blood, E013 doesn't bind even as much as the control. In short, Palinski does not disclose any antibodies that can detect both human MDA-modified LDL and human OxLDL, certainly not any antibodies as good as mAb-4E6 and mAb-8A2, and certainly not any assay as good as applicants'.

"[E]very element and limitation of the claimed invention ... [are not] found in a single prior art reference, arranged as in the claim. *Karsten*; *Scripps*; *Brown*. There simply is no anticipation by Palinski, and Winzor provides no help to the Examiner's argument.[4]

Office Action, ¶ 15(ll) – rejection – claims 56, 61-65, 67-71, and 73 – § 102(b) – alleged anticipation based on Kotani and Winzor

The Examiner asserts that Kotani antibody ML25 binds to both MDA-modified LDL and OxLDL, and the Examiner points to Kotani's Abstract, Figure 1, and page 123 ("Results"). However, as noted above, "[t]o anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim," and Kotani fails to disclose or even suggest numerous claim limitations. For example, Kotani's antibody ML25 does not bind with both human MDA-modified LDL and human OxLDL, and Kotani's ML25 is not applicants' mAb-4E6 or mAb-8A2 (or anything nearly as good as those antibodies). Thus, independent claim 56 (now cancelled) was not anticipated and neither is new independent claim 75.

First, the Abstract specifically notes that it is copper oxidized LDL, not physiological (human) LDL, that was supposedly "detectable." Second, Figure 1 shows that ML25's affinity for MDA-modified LDL is not high enough to meet the numerical threshold for "high affinity" as that term is used in the application (i.e., 5×10^8 M^{-1}; application, page 5, line 14 et seq.). Fifty percent inhibition by competitor MDA-modified LDL (data points shown by black circles) against plated MDA-modified LDL (B/B_0 = 50%) occurs at approximately 2.5×10^2 mg/l, which (using a molecular weight of

[4] The Examiner asserts, incorrectly, that Palinski is silent with respect to the binding affinities of the antibodies. As explained above, Palinski's curves provide the binding affinities, and those affinities are far lower than the binding affinities of mAb-4E6 and mAb-8A2, which are recited in the claims. The Examiner relies on Winzor for the proposition that affinity constants can range from 10^3 to 10^{15} M^{-1}. Even assuming that Winzor is correct, the Examiner's argument (that the affinities of Palinski's antibodies must be within the range claimed by applicants) is unsound. Even if some unidentified antibodies for some unidentified analytes *may* have sufficiently high affinity to meet the numerical minimum threshold for "high affinity" as that term is used in the application (i.e., 5×10^8 M^{-1}; application, page 5, line 14 et seq.), that certainly does not mean Palinski's particular antibodies are "high affinity" and, in fact, the two Palinski affinities calculated above are lower than applicants' threshold minimum value and far lower than the affinities of mAb-4E6 and mAb-8A2.

3,500,000[5]) yields an affinity constant of only about 1.4×10^7 M^{-1}. Moreover, as shown by the data points for copper oxidized LDL (data points shown by "x"), the binding affinity of ML25 to the copper oxidized LDL is even lower than ML25's binding affinity to MDA-modified LDL. In other words, ML25 does not have "high affinity" for either MDA-modified LDL or copper oxidized LDL. Third, the "Results" section on page 123 (which the Examiner cites) agrees with this conclusion, stating that "LDL oxidized with 10 μM Cu^{2+} for 2.5 h also competed, but less effectively [than any of several substances, including MDA-modified LDL]."

Kotani's antibody ML25 does not bind with both human MDA-modified LDL and human OxLDL, and Kotani's ML25 is not applicants' mAb-4E6 or mAb-8A2 (or anything nearly as good as those antibodies), as required by the claims.[6]

Office Action, ¶ 16(III) – rejection – claims 57-60 – § 103(a) – alleged obviousness based on Palinksi, Winzor, and Haberland

The Examiner asserts that the Palinski-Winzor combination differs from the substance of dependent claims 57-60 only in the number of lysine substitutions and, to try to remedy that defect, the Examiner adds Haberland. As demonstrated above, the Palinski-Winzor combination did not and does not disclose or suggest clear limitations in cancelled independent claim 56 or new independent claim 75 (e.g., determining human MDA-modified LDL and human OxLDL, the use of mAb-4E6 and mAb-8A2). Thus, contrary to what the Examiner asserts, the Palinski-Winzor combination differs by more than just the number of lysine substitutions. Applicants do not agree with the Examiner's reasoning underlying the rejection of claims 57-60 but to

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[5] See footnote 3.

[6] The Examiner asserts, incorrectly, that Kotani is silent with respect to the binding affinity; however, Kotani's Figure 1 provides the binding affinity of ML25, and that affinity is far lower than the binding affinities of mAb-4E6 and mAb-8A2, which are recited in the claims. The Examiner relies on Winzor for the proposition that affinity constants can range from 10^3 to 10^{15} M^{-1}. Even assuming that Winzor is correct, the Examiner's argument (that the affinity of ML25 must be within the range claimed by applicants) is unsound. Even if some unidentified antibodies for some unidentified analytes *may* have sufficiently high affinity to meet the numerical minimum threshold for "high affinity" as that term is used in the application, that certainly does not mean Kotani's particular ML25 antibody is "high affinity" and, in fact, the calculated ML25 affinity is lower than applicants' threshold minimum value (5×10^8 M^{-1}) and far lower than the affinities of mAb-4E6 and mAb-8A2.

avoid overburdening the record will simply note that the rejection of claims 57-60 was unsound because they depended from non-anticipated, non-obvious claim 56; claims 76-79 should not be similarly rejected.[7]

Office Action, ¶ 16(IV) – rejection – claim 74 – § 103(a) – alleged obviousness based on Palinksi, Winzor, and Kondo

The Examiner asserts that the Palinski-Winzor combination differs from the substance of dependent claim 74 only in "not teaching the detection of human MDA-modified LDL and human OxLDL detection at 0.02 mg/dl in undiluted human plasma" and, to try to remedy that defect, the Examiner adds Kondo. As demonstrated above, the Palinski-Winzor combination did not and does not disclose or suggest clear limitations in cancelled independent claim 56 or new independent claim 75 (e.g., determining human MDA-modified LDL and human OxLDL, the use of mAb-4E6 and mAb-8A2), so the Palinski-Winzor combination actually differs by more than just detection of any analytes at 0.02 mg/dl as asserted by the Examiner.

Applicants emphatically disagree with the Examiner's reasoning underlying the rejection of claim 74 but to avoid overburdening the record will simply make two points. First, the rejection of claim 74 was unsound because claim 74 depended from non-anticipated, non-obvious claim 56.[8] Second, Kondo (Daiichi EP 0 484 863) was discussed in the June 5, 2006 Response (see pages 12-18). There applicants explained in detail why Kondo did not disclose or suggest applicants' invention.[9] Applicants readopt all of their reasoning set forth in the June 5, 2006 Response as if fully set forth herein.[10]

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[7] Claim 56 was rejected as allegedly being anticipated by Palinski or Kotani, as evidenced by Winzor; there were no obviousness rejections of claim 56. For reasons set forth above, neither Palinski nor Kotani (regardless of Winzor) anticipated claim 56 or anticipates claim 75.

[8] See footnote 7.

[9] In Kondo: (a) there is no mention of detecting human OxLDL and (b) (i) the term "human MDA-modified LDL" is used by Daiichi to refer to its manufactured material and not to refer to actual physiological human MDA-modified LDL whereas (ii) applicants' claims use the term "human MDA-modified LDL" to refer to actual human MDA-modified LDL and not some artificial manufactured material. The substance being detected in the Kondo examples labeled as "human MDA-modified LDL" is Kondo's manufactured material and is not actual physiological human MDA-modified LDL. The Examiner again points to Antibody 29210 in Example 4 of the Daiichi application and asserts that Antibody 29210 has a "detection limit of less than 0.01 mg/dl MDA-modified LDL in an ELISA." However, Antibody 29210 was tested

[footnote cont'd ...]

Office Action, ¶ 16(V) – rejection – claims 57-60 – § 103(a) – alleged obviousness based on Kotani, Winzor, and Haberland

The Examiner asserts that the Kotani-Winzor combination differs from the substance of dependent claims 57-60 only in the number of lysine substitutions and, to try to remedy that defect, the Examiner adds Haberland. As demonstrated above, the Kotani-Winzor combination did not and does not disclose or suggest clear limitations in cancelled independent claim 56 or new independent claim 75 (e.g., determining human MDA-modified LDL and human OxLDL, the use of mAb-4E6 and mAb-8A2), so the Kotani-Winzor combination actually differs by more than just the number of lysine substitutions. Applicants do not agree with the Examiner's reasoning underlying the rejection of claims 57-60 but to avoid overburdening the record will simply note that because claims 57-60 depended from non-anticipated, non-obvious claim 56, their rejection was unsound; claims 76-79 should not be similarly rejected.[11]

Office Action, ¶ 16(VI) – rejection – claim 74 – § 103(a) – alleged obviousness based on Kotani, Winzor, and Kondo

The Examiner asserts that the Kotani-Winzor combination differs from the substance of dependent claim 74 only in "not teaching the detection of human MDA-modified LDL and human OxLDL detection at 0.02 mg/dl in undiluted human

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[...footnote cont'd]

against Daiichi's manufactured "human MDA-modified LDL," not against true human (physiological) MDA-modified LDL, and it was tested in BSA-PBS, not in undiluted human plasma. Note the use in applicants' claims of "sample derived from the body fluids or tissues of a human being" (e.g., claim 56), "human MDA-modified LDL" (e.g., claim 56), and "undiluted human plasma" (claim 74). Thus, claim 56 specified that human (i.e., physiological) MDA-modified LDL (and not Kondo's manufactured and misleadingly named "human MDA-modified LDL") was being detected and/or quantified in a sample derived from the body fluids or tissues of a human being. Furthermore, the Examiner has adduced no evidence that Kondo's antibodies have "high affinity" for true human MDA-modified LDL as required by those claims, particularly given how "high affinity" is defined in the application (see page 5, lines 14-24). In fact, from the discussion in the June 5, 2006 Response, it should be clear that there is no good evidence that Kondo's antibodies have high affinity for true human (physiological) MDA-modified LDL in any sample, whether or not derived from the body fluids or tissues of a human being.

[10] It is readily apparent that the Examiner has not met her burden for making a prima facie case for obviousness. See MPEP § 706.02(j) and the June 5, 2006 Response, e.g., pages 19-24.

[11] See footnote 7.

plasma" and, to try to remedy that defect, the Examiner adds Kondo. As demonstrated above, the Kotani-Winzor combination did not and does not disclose or suggest clear limitations in cancelled independent claim 56 or new independent claim 75 (e.g., determining human MDA-modified LDL and human OxLDL, the use of mAb-4E6 and mAb-8A2), so the Kotani-Winzor combination actually differs by more than just detection of any analytes at 0.02 mg/dl.

Applicants emphatically disagree with the Examiner's reasoning underlying the rejection of claim 74 but to avoid overburdening the record will simply make two points. First, the rejection of claim 74 was unsound because claim 74 depended from non-anticipated, non-obvious claim 56.[12] Second, Kondo (Daiichi EP 0 484 863) was discussed in the June 5, 2006 Response (see pages 12-18). There applicants explained in detail why Kondo did not disclose or suggest applicants' invention.[13] Applicants readopt all of their reasoning set forth in the June 5, 2006 Response as if fully set forth herein.[14]

* * *

CONCLUSION

Reconsideration and favorable action on the merits, including allowance of all the claims, are respectfully requested.

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[12] See footnote 7.
[13] See footnote 9.
[14] See footnote 10.

If the Examiner has any questions regarding this paper, she is respectfully requested to telephone the undersigned attorney if doing so would expedite prosecution of this case.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Mail Stop Amendment, Commissioner For Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on December 15, 2006
(Date of Deposit)

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